

## Chemotherapy in gastric cancer: a never ending saga

For a long period of time, gastric carcinoma was considered to be a poorly chemoresponsive tumor. Before the CT-scan era, clinical investigations were not reliable by today's standards because of the paucity of good radiological tools, and because patients without measurable disease were also enrolled. The so-called 'first-generation' drug combinations, designed before the introduction of cisplatin to the treatment of this disease, gave disappointing results [1–4]. The combination of mitomycin C, doxorubicin and 5-fluorouracil (5-FU) (FAM) was considered a standard for more than a decade.

In the late 1980s, attempts were made to increase the efficacy of chemotherapy by designing more intensive regimens. The combination of 5-FU–doxorubicin–methotrexate (FAMTX) with high-dose methotrexate (MTX) and leucovorin (LCV) rescue was designed in that spirit. This combination was shown, in a randomized fashion, to be superior to FAM with a response rate of 41% for FAMTX versus 9% for FAM, and a median survival of 42 weeks versus 29 weeks, respectively [5–7]. FAMTX became, therefore, the suggested European gold standard of the early 1990s. Other investigators introduced cisplatin in the treatment for gastric cancer. Cytotoxic regimens such as 5-FU–cisplatin (FUP), 5-FU–leucovorin–cisplatin (FLP), cisplatin–epirubicin–leucovorin–5-FU (PELF), etoposide–doxorubicin–cisplatin (EAP) or even etoposide–5-FU–leucovorin (ELF) were developed and originally shown to yield response rates (RRs) ranging from 37% to 72%, with median response durations of 4–7 months, according to the non-randomized phase II studies considered [8–13]. Unfortunately, results observed in subsequent randomized trials comparing second-generation regimens with each other, or with older treatment schemes were less convincing [13–16]. These results diminished the original enthusiasm arising from the excellent results of earlier phase II studies, and demonstrated the fragility of results based on monocentric or oligo-centric accruals [17]. These data also underscored the need for new approaches and for new active agents.

In the 1990s, two new approaches were investigated. The first consisted of increasing the efficacy by raising the dose intensity of the chemotherapy [18, 19]. An intensive weekly chemotherapy called EPFL, containing epirubicin, cisplatin, 5-FU and leucovorin, was studied in Italy and reported a 62% response rate in a large phase II trial of 105 patients [20]. However, toxicity was substantial, requiring regular use of colony-stimulating factors. The second approach, developed mainly at the Royal Marsden Hospital, UK, was based on new schedules of administration of 5-FU, as proposed by Lokich et al. in the treatment of colorectal cancer [18, 21]. A regimen of epirubicin, cisplatin and 5-FU

(ECF) in continuous infusion was developed in the UK. Impressive RRs as high as 71% with 12% complete responses (CR) were obtained in a phase II setting [22–24]. Compared with FAMTX, in a phase III randomized study, ECF yielded a higher RR (45% versus 21%,  $P = 0.0002$ ), a superior median time to progression (7.4 months versus 3.4 months) and an enhanced overall survival (8.9 months versus 5.7 months,  $P = 0.0009$ ). These data led the investigators to propose ECF as standard practice [25].

Over the last 5 years, several new drugs have been successfully tested against gastric cancer. Among them, we find the taxanes [paclitaxel (Taxol®) and docetaxel (Taxotere®)], the topoisomerase I inhibitor irinotecan, also called CPT-11 (Campto®), and, more recently, the cisplatin derivative oxaliplatin (Eloxatin®), known for having a profile of activity different from its parent compound. Other drugs such as oral 5-FU analogs and prodrugs, including S-1 and capecitabine (Xeloda®), might also be attractive for this indication in place of i.v. 5-FU [26–28]. Response rates of up to 65% were obtained in phase II studies evaluating taxane, irinotecan or oxaliplatin containing regimens [29–37]. They generated a large amount of enthusiasm despite median overall survivals still in the 10 month range. Randomized phase III trials intended to confirm these results are currently ongoing.

In this issue of *Annals of Oncology*, Kruijtz et al. present results of a phase II trial investigating the activity of oral paclitaxel in co-administration with cyclosporin A (CsA) as first-line treatment in patients with advanced gastric cancer [38]. The co-administration of CsA is aimed at blocking multidrug resistance (MDR) activity, which could interfere with paclitaxel intracellular efficacy, as well as at depressing the liver cytochrome P450 system involved in paclitaxel metabolism. At the expense of relatively little toxicity, they report an overall response rate of 32%, which is amazingly high for a single drug in this indication. The CsA contribution to these results, by whatever pharmacological pathway, is difficult to assess. In that respect, we can recall that pharmacological MDR modulation by CsA, verapamil and other drugs has been investigated for more than a decade without much clinically meaningful success so far [39–41].

Is the report by Kruijtz et al. simply another phase II report to take stock of in the metastatic gastric cancer saga? At first glance we could say "yes". However, even in the absence of data from randomized trials, if we look carefully at the results obtained in single-arm studies with new agents, we can extract some insight of improvement. One of the interesting issues is that many of these new agents have been shown to retain significant activity in second-line therapy [42–45]. Likewise, patients failing first-line treatment with these new drugs can still respond to another drug combination [46]. These observations open the way to second-line therapy for metastatic gastric cancer. As in breast cancer,

where many metastatic patients can benefit from different lines of treatment, some responding gastric cancer patients could now benefit from additional lines of systemic therapy based on these new agents. These new agents also offer us the possibility of providing patients with regimens better adapted to their condition. Both taxanes and irinotecan can now be given on a weekly basis, allowing a reduction in toxicity and the adaption of prescriptions according to patient tolerance.

The report by Kruijtz et al. brings another dimension to these 'little' improvements: the possibility to treat patients orally. Efficacy and tolerance seem to compare favorably with equivalent i.v. schedules. As mentioned above, some patients with metastatic gastric cancer will survive long enough to receive several lines of therapy. The availability of an oral regimen would be welcome and may enhance their quality of life. As pointed out by the authors, oral paclitaxel could be combined with capecitabine and provide a completely oral regimen. Oral CPT-11 is also presently being tested in phase I trials and could soon join the club of oral drugs available for gastric cancer.

It is unlikely that, even with positive randomized trial results, these new active agents will bring a significant breakthrough in the treatment of metastatic gastric cancer. They will, however, provide us with additional tools for a better management of this disease. Likewise, their integration into the multidisciplinary approach for the cure of resectable disease may be worthwhile and may need to be explored [47]. The never ending saga will go on, but, it may be somehow, a worthwhile saga.

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